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Health and Environmental Effects Profile for Simazine

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR SIMAZINE

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16. ABSTRACT

The Health and Environmental Effects Profile for Simazine was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for Simazine.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

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TABLE OF CONTENTS

		Page
1.	INTRODUCTION	1
1.1.	STRUCTURE AND CAS NUMBER	1
1.2.	PHYSICAL AND CHEMICAL PROPERTIES	1
1.3.	PRODUCTION DATA	2
1.4.	USE DATA	2
2.	ENVIRONMENTAL FATE AND TRANSPORT PROCESSES	3
2.1.	AQUATIC MEDIA	3
2.2.	AIR	6
2.3.	SOIL	6
3.	EXPOSURE	12
3.1.	WATER	12
3.2.	FOOD	13
3.3.	AIR	13
3.4.	DERMAL	14
4.	PHARMACOKINETICS	15
4.1.	ABSORPTION	15
4.2.	DISTRIBUTION	15
4.3.	METABOLISM	15
4.4.	EXCRETION	16
5.	EFFECTS	17
5.1.	CARCINOGENICITY	17
5.2.	MUTAGENICITY	18
5.3.	TERATOGENICITY	22
5.4.	OTHER REPRODUCTIVE EFFECTS	23
5.5.	CHRONIC AND SUBCHRONIC TOXICITY	23
5.6.	OTHER RELEVANT INFORMATION	24
6.	AQUATIC TOXICITY	25
6.1.	ACUTE	25
6.2.	CHRONIC	28
6.3.	PLANT EFFECTS	28
6.4.	RESIDUES	29
6.5.	OTHER RELEVANT INFORMATION	30

Page

7. GUIDELINES AND STANDARDS. 32

7.1. HUMANS 32
7.2. AQUATIC. 32

8. RISK ASSESSMENT 33

9. REFERENCES. 35

APPENDIX: LITERATURE SEARCHED. 49

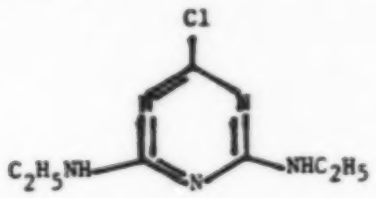
LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
bw	Body weight
CHO	Chinese hamster ovary
CNS	Central nervous system
DMSO	Dimethyl-sulfoxide
DNA	Deoxyribonucleic acid
EC_{50}	Median effective concentration
GC	Gas chromatography
GOT	Glutamic oxalacetate transaminase
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
MATC	Maximum acceptable toxicant concentration
ppm	Parts per million
TLC	Thin layer chromatography
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Simazine is the common name for 2-chloro-4,6-di(ethylamino)-1,3,5-triazine. Other chemical synonyms include 2-chloro-4,6-bis(ethylamino)-s-triazine and 6-chloro-N,N'-diethyl-1,3,5-triazine-2,4-diamine. The common trade names of this chemical in the United States and Europe are Princep, Aquazine, Gesatop and Primatol (WSSA, 1979). The structural and molecular formula for simazine are as follows:



Empirical formula: $C_7H_{12}ClN_5$

Molecular weight: 201.7

The Chemical Abstract Services (CAS) Registry number for simazine is 122-34-9.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Simazine is a white crystalline solid (WSSA, 1979). Selected physical and chemical properties of this compound are listed below (BCPC, 1977; WSSA, 1979; Plimmer, 1980 unless otherwise stated).

Melting point:	225-227°C
Vapor pressure:	6.1×10^{-9} mm Hg at 20°C
Solubility:	5 mg/ℓ in water at 20°C 400 mg/ℓ in methanol at 20°C 2 mg/ℓ in petroleum ether at 20°C 900 mg/ℓ in chloroform at 20°C

Stability:	stable in neutral and slightly acidic on basic media, but hydrolyzed by stronger acids and
Log octanol-water partition coefficient: (log K_{ow}):	2.16 (Brown and Flagg, 1981) 1.51 (Briggs, 1981)
Log soil sorption coefficient standardized with respect to soil organic carbon (log K_{oc}):	2.13 (Kenaga, 1980) (calculated from an empirical equation from water solubility data) 2.33 (Brown and Flagg, 1981)

pK = 1.65 (Dubach, 1970)

The amino groups of simazine are not very reactive and normal acylating agents do not acylate this compound. An N-nitroethylamino derivative has been obtained from simazine (Plimmer, 1980).

1.3. PRODUCTION DATA

Simazine is made by the reaction of cyanuric chloride with ethylamine in the presence of an acid acceptor (BCPC, 1977). Both SRI (1983) and USITC (1982) list Ciba-Giegy Corp., St. Gabriel, LA, as the only producer of this chemical in the United States. However, the present annual United States' production data of this chemical are not available.

1.4. USE DATA

Simazine is used as a pre-emergence herbicide for the control of broad-leafed and grassy weeds in deep-rooted crops such a corn, cotton, sorghum, sugar cane, asparagus, broad beans, grape vines, ornamental and forest nurseries, coffee, tea and cocoa. It is also very promising for the control of submerged vegetation and algae in farm ponds, fisheries, etc. (BCPC, 1977; Plimmer, 1980).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. AQUATIC MEDIA

The photolysis of simazine in solution has been studied by several investigators. Pape and Zabik (1972) irradiated simazine in methanol, 1-butanol, 1-octanol and 1-decanol in borosilicate glass at wavelength >290 nm. The dechlorinated and carbon-2-n-alkoxy products were definitely identified as the reaction products. For example, simetone was one of the products of photolysis of simazine in methanol.

The irradiation of simazine in saturated aqueous solution at pH 4.0 and in the presence of riboflavin (0.3 mole riboflavin/mole simazine) as a photosenzitizer was studied by Retjo et al. (1983). When photoreactions were carried out with direct outdoor sunlight or in a laboratory with a daylight lamp, simazine produced N-deethylation products. The 2-chloro-4,6-diamino-s-triazine formed was further oxidized to unidentified products. However, these investigators failed to detect any 2-hydroxy derivatives even after exposure for several days to sunlight or daylight lamp. The reaction rate was observed to increase with the lowering of pH. This was explained as due to the ability of riboflavin to abstract hydrogen at a pH lower than neutral.

The photochemistry of simazine in methanol and butanol solution at 300 nm and 40°C was also studied (Ruzo et al., 1973). A decrease in the rate constant (K) was observed when n-butyl alcohol was used instead of methanol or water. In aqueous solution, the photoreaction was found to follow a zero-order rate, and in 10^{-5} mole ℓ^{-1} solution, the rate constant was determined to be 0.66×10^{-10} mole ℓ^{-1} sec^{-1}. Assuming the half-life ($t_{1/2}$) to follow the equation, $t_{1/2} = 1/2\ (Ao/k)$, where Ao is the initial concentration, the half-life for photoreaction from a 10^{-5} molar

solution can be calculated to be <1 day. It should be noted that the half-life for a zero-order reaction is directly proportional to the initial concentration of the substrate.

The possibility of the hydrolysis of simazine in aquatic media has not been comprehensively studied. The half-life of simazine hydrolysis in aqueous medium has been calculated to be 40 days at pH 2 (Helling, 1970). From the soil hydrolysis study of Kaufman and Kearney (1970), it can be speculated that simazine hydrolysis may also be significant at basic pH of >8.4. Hydrolysis may not be significant at neutral or near neutral pHs. Increase in temperature at high or low pH may also increase the rate of hydrolysis (Kaufman and Kearney, 1970).

The rate of biodegradation of simazine in natural aquatic media is not known. Based on the ability of soil microorganisms to degrade simazine (see Section 2.3.), it can be speculated that biodegradation of this compound in aquatic media will take place. However, this process is not likely to contribute significantly to the disappearance of simazine in natural aquatic media.

Few investigators have studied the loss of simazine from aquatic media via physical processes. The volatility of deposited simazine from a metal surface (planchets) was found to be small. At 25°C, virtually no loss of simazine was observed in 6 hours (Jordan et al., 1970). Simazine was also found to be less volatile from moist soil than dry soil (Jordan et al., 1970). When these two observations are considered, it can be speculated that the loss of simazine through volatility from aquatic media will not be significant.

The loss of simazine by sorption and subsequent sedimentation in water bodies has not been studied in detail. If one considers the soil adsorption

characteristics (see Section 2.3.) and the K_{oc} value of this compound, it can be predicted that sorption may be a significant process. This observation can be supported by the study of Lopez-Avila and Hites (1980), who monitored water and sediments from Pawtucket River, RI, for contaminants arising from a small specialty chemicals manufacturing plant. Although no simazine could be detected in the water, the concentration of the compound was found to vary between 2 and 1600 ppm in the river sediment.

The overall persistence of simazine in aquatic media has not been studied extensively. In one study, the half-life of simazine added at concentrations of 0.25 and 0.50 ppm to pond water was reported to be 7 days after the fourth weekly addition of simazine (Sheets, 1970). It should be emphasized that the half-life of simazine in aquatic media may vary depending on the characteristics of the water body. Thus, the half-life may be different in pond, river and lake waters.

The bioaccumulation of ^{14}C-labeled simazine in mosquito fish, Gambusia affini, was studied in a freshwater micro-ecosystem (Isensee and Yockim, 1980). In a model static ecosystem, the BCF of simazine and its ^{14}C-labeled metabolites were found to vary between 19 and 50, whereas in a flowthrough system, the same parameter varied between 0 and 6765. The wide variation in the flowthrough system was due in part to a malfunction of the dosing apparatus. Thin-layer chromatography or fish homogenates showed that 30-70% and 100% of the radioactivity was in the form of metabolite in the static and flowthrough systems, respectively. Rogers (1970) reported that green sunfish, Lepomis cyanellus, contained 0.95 and 2.29 ppm simazine after 3 weeks of exposure to 1 and 3 ppm, respectively. No simazine residues were detected in fish after 7 days in clean water. Mauck et al. (1976) investigated the residue dynamics of simazine in small ponds. They found that

residue concentrations in bluegills generally did not exceed the concentrations of simazine in the water from which the fish were taken; however, low levels of simazine were detected in fish for ~1 year after the last pond treatment.

These results indicate that simazine probably has a low biocentration potential, but may persist in the aquatic environment for extended periods.

2.2. AIR

Specific data regarding the fate or transport of simazine in the atmosphere were not located in the available literature. Data summarized in Sections 2.1. and 2.3. suggest that photodegradation of simazine in the atmosphere could be one of the significant pathways for the loss of this compound. It has been suggested by Cuppitt (1980) that adsorption will be a reasonable vapor-phase removal mechanism only for chemicals with saturation vapor pressure $\leq 10^{-7}$ mm of Hg. Since the vapor pressure of simazine at 20°C is 6.1×10^{-9} mm Hg, this compound is expected to remain strongly sorbed to particulate matter in the air.

2.3. SOIL

The fate and transport of simazine in soil has been more adequately studied than its fate and transport in atmosphere and aquatic media. The two likely chemical processes that may cause disappearance of this compound from soils are hydrolysis and photodecomposition. Hydrolysis of simazine to the 2-hydroxy derivative has been predicted to be the dominant factor at high temperatures (>30°C) and at pH values >8.5 and <5.5 (Kaufman and Kearney, 1970). This dependence of hydrolytic half-life on soil pH has been demonstrated well in the case of atrazine (Jordan et al., 1970). Although no quantitative data are available, it can be stated that chemical hydrolysis of simazine in soils in the pH range of 5.5-8.5 and at temperatures <25°C may not be a very active process (Weber, 1970).

The photodecomposition of simazine deposited on aluminum planchets with UV light sources of peak emission of 254, 311 and 360 nm and at 42° has been reported by Jordan et al. (1970). The photodecomposition was found to increase as the wavelength of irradiation was decreased. At 311 nm, the half-life of simazine photodecomposition was ~20 days. On the other hand, when simazine sprayed on soil was exposed to sunlight, the loss from irradiation was found to be only 25% in 25 days (Jordan et al., 1970). Therefore, photodecomposition of simazine under natural sunlight would appear to be unimportant. This is not surprising in view of the fact that simazine absorbs at ~220 nm, and natural sunlight produces little radiant energy <290 nm (Kearney, 1970). Therefore, the slight photodecomposition of simazine observed at 311 nm may be due to photolysis through sensitization, although the specific sensitizer has not been identified (Jordan et al., 1970).

The biodegradability of simazine in soils has been studied by several investigators. Fournier and Catroux (1980) showed that a number of isolated microorganisms, including Aspergillus flavus, Aspergillus fumigalus, Aspergillus niger, Penicillium rugulosum and Pseudomonas striata degraded simazine. Biodegradation of simazine was also observed with one clayish soil suspension. The microbial degradation of simazine in soils was also reported by Kaufman and Kearney (1970). These authors compiled a list of several soil microorganisms effective in the degradation of simazine. With a soil-solution enrichment culture, the microbial degradation of simazine was reported to be <20% in 10 days (Kaufman and Kearney, 1970). The rate-limiting process was speculated to be physical or chemical in nature rather than biological. The slow rate of breakdown might be due to the effects of adsorption-desorption equilibrium on the availability of simazine for uptake

and metabolism by soil microorganisms. Soil temperature, pH, moisture content and organic matter content may all affect the activities of soil microorganisms. Both microbial and chemical degradation are enhanced by moisture. Excessive moisture would retard decomposition by aerobes and enhance decomposition by anaerobes (Sheets, 1970). Soil bacteria and actinomycetes enhance biodegradation in near neutral or alkaline moist soils, whereas fungi are generally more active under low moisture and pH levels (Kaufman and Kearney, 1970). Soil microorganisms, on the other hand, are generally more active in soils having high organic matter content than in soils having low organic matter contents. Therefore, biodegradation should be faster in soils containing high organic matters (Kaufman and Kearney, 1970). The effect of simazine half-life on soil organic content was reported by LeBaron (1970). Addition of 1, 5 and 10% leaf compost to a sandy loam soil decreased the half-life of simazine to 140, 60 and 40 days, respectively. Without the leaf compost, the half-life was reported to be 105 days.

The metabolic products of microbial degradation of simazine in soil were studied with a C^{14} ring and chain or Cl^{36}-labeled simazine (Kaufman and Kearney, 1970). The metabolic products identified were 2-chloro-4-amino-6-ethylamino-s-triazine and probably 2,4-dihydroxy-6-amino-s-triazine.

The transport of simazine from soil by physical processes, such as leaching, runoff and evaporation has been extensively studied. The leachability of simazine from soil is related to its soil adsorption capability. Adsorption of simazine increased as titratable acidity, organic matter and, to a lesser extent, clay content of soil increased (Weber, 1970; Helling, 1970). The cation exchange capacity of clay may be responsible for the adsorption dependence of soil on clay content (Helling, 1970). Decrease in

soil temperature also increased adsorption of simazine (Bailey and White, 1970). Weber (1970) proposed that a weakly basic herbicide such as simazine would be protonated in acid soil systems and ionically adsorbed by negatively charged soil colloids. This may result in increased leaching of simazine as the soil pH decreases.

The mobility of simazine in soil was determined by Helling and Dragun (1981) by means of soil TLC and soil column leaching experiments. They determined that simazine has a low to intermediate mobility in silty clay loam and clay loam soils (R_f of 0.17-0.36). This low to intermediate mobility of simazine has been established by a number of investigators who demonstrated that simazine residue in soil does not penetrate more than 30 cm inside soils (Fryer et al., 1980; Hance et al., 1981; Smith et al., 1975; Grover et al., 1980; Khan and Marriage, 1979; Hogue et al., 1981). Burnside et al. (1963), on the other hand, detected simazine at a depth of >60 cm in one silty clay loam and a loam soil 16 months after the application of the herbicide. It should be remembered that in addition to being affected by soil characteristics, leachability increases with the frequency of rainfall and decreases with rainfall intensity (Burnside et al., 1961), and increases with higher application rates (Helling, 1970).

The transport of simazine in runoff from conventional and non-tillage fields was studied by Triplett et al. (1978). These investigators found that the highest concentration of simazine was present in runoff occurring soon after application and declined rapidly thereafter. The quantity of simazine transported increased with the amount of runoff and was inversely related to the length of time between application and the runoff event. A maximum of ~5% of applied simazine was transported in the runoff under the

most favorable conditions. For most fields, the amount transported was <1% of the total applied. Less runoff was observed from non-tillage than from conventional fields.

The loss of simazine through volatility from soil was reported by Jordan et al. (1970). These investigators reported <10% loss of simazine in 3 days from five different soils at 35°C. The loss of simazine through volatilization was <20% in 3 days at 45°C. Soil type had little effect on loss of simazine via volatility.

Finally, the persistence of simazine as a result of all the chemical microbial and physical processes was studied by a number of authors. As has been discussed earlier, the soil persistence was found to depend on soil temperature, moisture content, soil type (particularly its organic content), soil pH and the amount and frequency of rainfall (Smith et al., 1975; Smith and Hayden, 1976; Rahman and Matthews, 1979; Slack et al., 1978; Walker, 1978; Jensen and Kimball, 1982; Nearpass et al., 1978). The overall half-life of simazine in soils was estimated to be 33-44 days at average soil temperatures varying between 13 and 21°C by Nearpass et al. (1978). Sheets (1970) reported a value of 20 days for the half-life of simazine at a soil temperature of 18°C. Using data compiled from the literature on the concentrations of simazine observed in runoff water, Wauchope and Leonard (1980) predicted a half-life of 20 days for simazine in soil. The semi-empirical formula used for the estimation of half-life did not include the effect of temperature on the estimated half-life.

The distribution of simazine in a terrestrial model ecosystem was studied by Gile et al. (1980) and Metcalf et al. (1979). In the model ecosystem of Gile et al. (1980), ^{14}C ring-labeled simazine was applied as a foliage spray. The following percent of applied radioactivity was recovered in

different phases by 20 days post-treatment: 43% on plants, 35% in soils, 21% in air, 0.8% in animals and 0% in groundwater. In a somewhat different model ecosystem, also using ^{14}C ring-labeled simazine, Metcalf et al. (1979) reported the following terminal (27 days) environmental distribution of simazine plus metabolites: 12.8% in air, 76.5% in soil, 8.2% in water, 0.02% in aquatic animals and 2.5% in terrestrial animals. In the study by Metcalf et al. (1979), the plants were either consumed or demolished by the animals, and the residue was distributed among animals, air and soil. The identity of the ^{14}C-residues was not determined in either study.

3. EXPOSURE

3.1. WATER

Fifteen days after the application of simazine at a rate of 2.24 kg/ha, the concentration of simazine in runoff sample (water and sediment mixture) was reported to be 300 µg/ℓ (Wauchope and Leonard, 1980). The levels of simazine in water collected from 11 agricultural watersheds merging into Lake Huron, Lake St. Clair, Lake Erie and Lake Ontario between 1975 and 1977 were reported by Frank et al. (1982) and Konasewich et al. (1978). Simazine was detected (detection limit of <0.04 µg/ℓ) in ~9% of the water at a mean concentration of 0.05 µg/ℓ, and a concentration range of none detected to 3.4 µg/ℓ. Frank et al. (1979a) also monitored 39 streams flowing into Lake Ontario in 1977 for simazine level. Only 28% of the stream waters had detectable levels of simazine (detection limit 0.03 µg/ℓ). The mean concentration of simazine in all the water samples was 0.3 µg/ℓ with a concentration range of none detected to 6.0 µg/ℓ.

The level of simazine in 17 central European waters collected during 1976-1977 was measured by Hormann et al. (1979). In 5 of the 17 water samples, simazine was not detected (detection limit <0.4 µg/ℓ). Simazine was detected in the rest of the samples at concentrations varying from 0.4-10 µg/ℓ. The concentration of simazine in Pawtucket River, RI, originating from a small specialty chemical manufacturing plant, was reported by Lopez-Avila and Hites (1980). Although no simazine as detected (no detection limit given) in the river water, the river sediment contained between 2 and 1600 mg/kg of simazine. The U.S. EPA STORET Data Base reports the analysis of simazine in 1243 surface water and 195 whole water (water and sediment) samples. The mean concentration of simazine in the water samples was reported to be 0.03 µg/ℓ with a range of concentration of

none detected to 25 µg/ℓ. The mean concentration and the concentration range in whole water were reported to be 0.3 µg/ℓ, and none detected to 25 µg/ℓ, respectively.

Over the period 1968-1978, the waters from a large number of contaminated wells were analyzed for simazine levels by Frank et al. (1979b). Five of the 159 wells were found to be contaminated by simazine. Although the levels of simazine in four wells were in the concentration range of 0.1-10 µg/ℓ, one well showed a concentration as high as 12.6 mg/ℓ of simazine. The only available report of the occurrence of simazine in finished drinking water comes from Keith et al. (1976). These investigators reported a level of <0.1 µg/ℓ of simazine in the finished drinking water from the New Orleans area, collected in 1974.

3.2. FOOD

Simazine is absorbed mostly through plant roots with little or no foliage penetration and is readily washed from foliage by rain. Following root absorption, it is translocated and accumulated in the apical meristems and leaves of plants (WSSA, 1979). Although biotransformation of simazine may occur in plants (Sheets, 1970), it is reasonable to assume that some residue level may occur in sprayed agricultural products. However, specific data on the levels of simazine residues in harvested crops were not located in the literature. It has also been shown (see Section 2.1.) that simazine could be bioacccumulated in fish. Therefore, exposure of simazine from edible aquatic organisms could occur, although experimental data providing evidence for this could not be found in the literature searched.

3.3. AIR

It has been discussed in Section 2.8. that the terrestrial model ecosystem studies of radioactively labeled simazine show that between 12.8 and

21% of the applied radioactivity is distributed in the air. The identity of this volatile material was not determined. Pertinent monitoring data regarding the levels of simazine in air were not available in the literature searched.

3.4. DERMAL

Pertinent data regarding the dermal level of exposure to simazine were not located in the literature.

4. PHARMACOKINETICS

4.1. ABSORPTION

Metabolism and urinary excretion data indicate that simazine is absorbed from the gastrointestinal tract of rats (Sections 4.3. and 4.4.) (Bradway and Moseman, 1982). Further details regarding the actual levels of simazine observed in blood plasma or the kinetics of absorption were not found in the available literature.

4.2. DISTRIBUTION

In the abstract of a study from the Russian literature, it was reported that simazine was found in lambs of ewes treated during pregnancy (route and duration not reported in abstract) with simazine at a level of 1.4 mg/day (Nikov and Mikhailov, 1979). It was not indicated whether the transfer was transplacental or through the mothers' milk.

4.3. METABOLISM

Bradway and Moseman (1982) administered simazine by gavage to rats (300 g males) in doses of 0, 0.005, 0.05, 0.5, 5 or 50 mg/day for 3 days. Two urinary metabolites, 2-chloro-4-amino-6-(ethylamino)-s-triazine (I) and 2-chloro-4,6-diamino-s-triazine (III), were detected (by a GC equipped with an N-P detector) in rats treated with $\geq$0.5 mg/day of simazine. Metabolite III was detected at a much higher level in urine than metabolite I.

Khan et al. (1979) reported that a mixture of simazine and atrazine was metabolized <u>in vitro</u> by an unspecified enzyme in the 105,000 g soluble fraction of goose, pig and sheep liver homogenates. Metabolism occurred via hydrolysis and partial N-dealkylation (of only one alkyl group).

Conjugation of simazine by mouse liver glutathione S-transferase has been demonstrated in an <u>in vitro</u> study (Guddewar and Dauterman, 1979). Experiments with related 1,3,5-triazines suggested that a chloro group at the 2-position may be required for conjugation.

4.4. EXCRETION

The metabolism data of Bradway and Moseman (1982) (see Section 4.3.) indicate that metabolites of simazine are at least partially excreted via the urine. Further details regarding specific total volumes of excretion via urine or other routes were not available.

5. EFFECTS

5.1. CARCINOGENICITY

Donna et al. (1981) tested the carcinogenicity of Fogard S, a herbicide containing 37.5% simazine and 25% atrazine as active ingredients, to Swiss albino female mice. Groups of 25 mice were given either 13 subcutaneous or 13 intraperitoneal injections at 3-day intervals of 0.25 mℓ of a solution of Fogard S in 9% saline, which contained 2 mg/ℓ of the active ingredients. The total dose was 0.0065 mg of active ingredients. The control groups consisted of two groups of 50 mice given either 13 subcutaneous or 13 intraperitoneal injections at 3-day intervals of 0.25 mℓ of 9% saline solution. One animal/group was killed at 15-day intervals starting 1 month after the end of treatment. At 7 months from the beginning of treatment, all remaining animals were killed. Of the 25 mice receiving 13 subcutaneous injections of Fogard S solution, three animals had malignant lymphomas and one had peritoneal mesothelioma (for total tumor incidence as compared with controls, $p=0.00113$); one treated animal that had been cannibalized was not necropsied. There were no cases of malignant lymphoma or peritoneal mesothelioma among the 50 control animals. Of the 25 mice receiving 13 intraperitoneal injections of Fogard S solution, two animals had malignant lymphomas ($p=0.02661$) as compared with 0 of 50 for control animals; five of the treated animals were not necropsied because they had been cannibalized. Donna et al. (1981) indicated that their group is performing a cancer bioassay with pure simazine, larger numbers of animals and exposure by the oral route.

5.2. MUTAGENICITY

Simazine has been tested for genotoxicity in many prokaryotic and eucaryotic assays. These assays are summarized in Table 5-1. As can be seen in Table 5-1, simazine was positive only in gene mutation assays in eucaryotic systems.

Simazine was negative in the reverse mutation assay and rec-assay, using Salmonella typhimurium as the indicator organism, both in the absence and presence of external mammalian metabolic activation (Simmon et al., 1976; Eisenbeis et al., 1981; Waters et al., 1982; Ercegovich and Rashid, 1977; Andersen et al., 1972; Lusby et al., 1979; Nishimura et al., 1982). Negative results were also obtained in reverse and forward mutation assays with Escherichia coli (Waters et al., 1982; Fahrig, 1974), rec-assay with Bacillus subtilis (Shirasu et al., 1976; Shirasu, 1975) and reverse mutation assay with Serratia marcesceus (Fahrig, 1974); the addition of a mammalian metabolic activation system had no effect on these negative results. Simazine was negative in several gentoxicity assays using Saccharomyces cerevisiae with and without mammalian metabolic activation, including reverse mutation (Waters et al., 1982; Riccio et al., 1981), mitotic recombination (Waters et al., 1982; Simmons et al., 1976; Riccio et al., 1981), mitotic gene conversion (Fahrig, 1974; Riccio et al., 1981; Siebert and Lemperle, 1974; Waters et al., 1982) and mitotic crossing-over (Waters et al., 1982; Riccio et al., 1981).

Results of studies of sex-linked recessive lethal assays with Drosophila melanogaster are equivocal, with two reporting positive results (Waters et al., 1982; Valencia, 1981) and the other two reporting negative results (Benes and Sram, 1969; Murnik and Nash, 1977). Exposure of D. melanogaster to simazine results in a significantly increased incidence of dominant

TABLE 5-1

Genotoxicity Testing of Simazine

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response[a]	Reference
Reverse mutation	Salmonella typhimurium 5 strains, NOS	NR	NR	±S9	-	Simmon et al., 1976
Reverse mutation	S. typhimurium	spot test	10 µl/plate	±S9		Eisenbeis et al., 1981
	TA98				-	
	TA100				-	
	TA1535				-	
	TA1537				-	
	TA1537				-	
	TA1538				-	
Reverse mutation	S. typhimurium	plate incorporation	6 concentrations <10 mg/plate	±S9		Waters et al., 1982
	TA98				-	
	TA100				-	
	TA1535				-	
	TA1537				-	
	TA1538				-	
Reverse mutation	S. typhimurium	NR	NR	±S9		Nishimura et al., 1982
	TA98				-	
	TA100				-	
Reverse mutation	S. typhimurium 5 strains, NOS	NR	NR	None	-	Ercegovich and Rashid, 1977
Reverse mutation	S. typhimurium 8 strains, NOS	spot test	~1-5 µl/plate	None	-	Andersen et al., 1972
Reverse mutation	S. typhimurium	NR	NR	None		Lusby et al., 1979
	TA98				-	
	TA100				-	
	TA1535				-	
	TA1538				-	
Differential toxicity rec-assay	S. typhimurium SL4525(rec$^+$)/SL4700(rec$^-$) TA1978(rec$^+$)/TA1538(rec$^-$)	spot test	NR	±S9	-	Waters et al., 1982
					-	
Reverse mutation	Escherichia coli trp$^-$	NR	6 concentrations <10 mg/plate	±S9	-	Waters et al., 1982
	uvrA$^-$				-	
Forward mutation	E. coli Gal R^S	spot test	NR	None	-	Fahrig, 1974

0554D

06/07/84

TABLE 5-1 (cont.)

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response[a]	Reference
Foward mutation	E. coli	liquid holding test	NR	None	-	Fahrig, 1974
Relative toxicity	E. coli	NR	NR	±S9	+	Simmon et al., 1976
Rec-assay	Bacillus subtilis H17 Rec$^+$ M45 Rec$^-$	spot test	NR	None	 - -	Shirasu et al., 1976; Shirasu, 1975
Relative toxicity	B. subtilis	NR	NR	None	-	Simmon et al., 1976
Reverse mutation	Serratia marcescens a 21 a 742	spot test	NR	None	 - -	Fahrig, 1974
Reverse mutation	Saccharomyces cerevisiae strain D7	NR	5 concentrations NOS	±S9	+	Waters et al., 1982
Reverse mutation	S. cerevisiae strain D7	NR	NR	NR	-	Riccio et al., 1972
Mitotic recombination	S. cerevisiae strain D7	cell culture	5 concentrations NOS	±S9	+	Waters et al., 1982
Mitotic recombination	S. cerevisiae diploid strain, NOS	NR	NR	±S9	+	Simmon et al., 1976
Mitotic recombination	S. cerevisiae strain D3	NR	NR	±S9	+	Riccio et al., 1981
Mitotic gene conversion	S. cerevisiae	liquid holding test	NR	None	-	Fahrig, 1974
Mitotic gene conversion	S. cerevisiae strain D7	NR	NR	±S9	+	Riccio et al., 1981
Mitotic gene conversion	S. cerevisiae diploid strain, NOS	cell culture	1000 ppm	None	-	Siebert and Lemperle, 1974
Mitotic gene conversion	S. cerevisiae strain D7	cell culture	NR	±S9	+	Waters et al., 1982
Mitotic crossing-over	S. cerevisiae strain D7	cell culture	NR	±S9	+	Waters et al., 1982
Mitotic crossing-over	S. cerevisiae strain D7	NR	NR	±S9	+	Riccio et al., 1981

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TABLE 5-1 (cont.)

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response[a]	Reference
Sex-linked recessive lethal	Drosophila melanogaster	NR	NR	None	+	Waters et al., 1982
Sex-linked recessive lethal	D. melanogaster	males were exposed by feeding, with probable contact and inhalation exposures also	NR	None	+,-[b]	Valencia, 1981
Sex-linked recessive lethal	D. melanogaster	abdominal injection	0.005%	None	-	Benes and Sram, 1969
Sex-linked recessive lethal	D. melanogaster	by injection or by larval feeding	NR	None	-	Murnik and Nash, 1977
Dominant lethal	D. melanogaster	NR	NR	NR	+[c]	Murnik, 1976
Dominant lethal	D. melanogaster	by injection or by larval feeding	NR	NR	+[c]	Murnik and Nash, 1977
Nondisjunction and chromosomal loss	D. melanogaster	NR	NR	NR	+	Murnik 1976
Chromosome breakage, nondisjunction, and loss	D. melanogaster	by injection or by larval feeding	NR	NR	-	Murnik and Nash, 1977
Forward mutation	mouse lymphoma cells	cell culture	NR	±S9	+[d]	Waters et al., 1982
Sister chromatid exchange	CHO cells	cell culture	5 dilutions, NOS	±S9	-	Waters et al., 1982
Unscheduled DNA synthesis	human lung fibroblasts	cell culture	5 concentrations NOS	±S9	-	Waters et al., 1982
Mouse micronucleus	male Swiss-Webster mice	by gavage or i.p. to eight mice	NR	None	-	Waters et al., 1982

[a]Responses: +, positive; -, negative; ±, negative with and without S9 activation system

[b]Simazine was considered to be a weak mutagen in the sex-linked recessive lethal assay with D. melanogaster (Valencia, 1981).

[c]The positive response observed for simazine in dominant lethal assay with D. melanogaster may have been due to physiological toxicity to the sperm (Murnik, 1976; Murnik and Nash, 1977).

[d]Waters et al. (1982) did not indicate whether simazine was positive in the absence and/or presence of a mammalian metabolic activation system; rather, it was only indicated that simazine was tested with and without the external source of metabolic activation and that simazine gave a positive response in the forward mutation mouse lymphoma assay.

NR = Not reported; NOS = Not otherwise specified; i.p. = Intraperitoneal

lethal mutations; however, these positive responses may have been due to physiological toxicity to the sperm (Murnik, 1976; Murnik and Nash, 1977). Murnik (1976) reported positive results for simazine in a nondisjunction and chromosomal loss assay in D. melanogaster. A paper published later by Murnik and Nash (1977), however, indicated negative results for simazine in the same assay system. Simazine was positive in the mouse lymphoma forward mutation assay (Waters et al., 1982), but was negative in two other mammalian cell culture assays for sister chromatid exchange in CHO cells (Waters et al., 1982) and for unscheduled DNA synthesis in human lung fibroblasts (Waters et al., 1982). Simazine was negative in the in vivo mouse micronucleus assay following gavage or intraperitoneal dosing (Waters et al., 1982).

5.3. TERATOGENICITY

No teratogenic effects were observed in the fetuses of rats (10/exposure level) exposed to simazine aerosols of 17±12, 77±56, or 317±89 mg/m³ for 2 hours/day on days 7-14 of gestation (Dilley et al., 1977; Newell and Dilley, 1978). The simazine was dissolved in DMSO prior to aerosol generation. Control groups consisted of 19 untreated, 10 air-exposed and 10 DMSO-exposed pregnant rats. The dams were sacrificed on day 20 of gestation, at which time no gross pathological changes were seen in either dams or their fetuses. Treatment with simazine did not result in depression of maternal body weight or an increased number of resorptions, as compared with control animals. Fetal body weights in all three exposure groups were depressed significantly ($p<0.01$) relative to controls, but the depression was not dose-related. A significantly ($p<0.01$) decreased degree of caudal ossification was observed for the lowest and highest exposure levels. At the mid-exposure level, the degree of caudal ossification was less than controls, but not to a statistically significant degree.

5.4. OTHER REPRODUCTIVE EFFECTS

Following administration of simazine per os as a single dose of 1000 mg/kg bw to male mice, Seiler (1977) did not observe an inhibition of testicular DNA synthesis, which was measured as a function of depressed thymidine incorporation into DNA.

Following oral doses of simazine to sheep at levels of 6.0 mg/kg/day for 142 days or 25 mg/kg/day for 37-111 days, Dshurov (1979) observed necrobiotic and dystrophic changes in the testicular germinal epithelium and spermatogenetic changes. Further details regarding effects and the use of control animals were not provided in the available abstract of this Bulgarian study.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Dshurov (1979) administered simazine orally to sheep at levels of 1.4 mg/kg/day for 90-129 days, 3.0 mg/kg/day for 63-65 days, 6.0 mg/kg/day for 142 days, 25 mg/kg/day for 37-111 days, 50 mg/kg every 7 days for 153 days, or 100 mg/kg every 7 days for 153 days. This study from the Bulgarian literature was available only as an abstract; therefore, pertinent data, such as the use of control animals, were not reported. Animals were examined for histological organ changes at various times throughout the exposures. Changes observed include fatty and granular liver degeneration, diffuse granular kidney degeneration, neuronophagia, diffuse glial proliferation and degeneration of ganglion cells in the cerebrum and medulla; these effects were not associated with specific dose levels in the available abstract. At autopsy, spongy degeneration, hyperemia and edema were seen in the cerebrum of sheep that died; these effects varied with amount and duration of exposure, but were not associated with specific dose levels in the available abstract. Animals given 1.4 mg/kg/day had thyroid hypofunction, while "very marked" thyroid hypofunction and colloid goiter were observed in

animals given 6.0 mg/kg/day. At both the 6.0 and 25 mg/kg/day dose levels, necrobiotic and dystrophic changes in the testicular germinal epithelium and spermatogenetic changes were observed. Parenchymatus goiter was seen in sheep given simazine at a dose level of 50 or 100 mg/kg every 7 days for 153 days.

5.6. OTHER RELEVANT INFORMATION

The oral LD_{50} of simazine to rats is 5000 mg/kg and the intravenous LD_{50} to mice is 100 mg/kg (NIOSH, 1983). The oral LD_{50}s of simazine to two species of microtine voles, Microtus orchrogaster and M. canicaudus, are 3920 and 2010 mg/kg, respectively, for males and 3250 and 2360 mg/kg, respectively, for females (Cholakis et al., 1981).

Open application of 500 mg of simazine to the skin of rabbits resulted in irritation. A dose of 80 mg of simazine caused irritation to rabbits' eyes (NIOSH, 1983).

Several enzymatic changes occurred in male mice following an intraperitoneal injection of 5 mg simazine/kg bw (Joshi and Tewari, 1980). These effects included decreased levels of hepatic GOT, and both brain and hepatic alkaline phosphatase, and increased levels of hepatic glutamate pyruvate transaminase, renal GOT, hepatic aldolase, hepatic peroxidation, hepatic membrane damage and enzymes released into the blood.

Two-day dietary feeding of simazine (level not reported in the available abstract) resulted in increased protein-bound, free and total concentrations of 11 oxyketosteroids in the blood of treated wild house mice (Kamenov and Zolotarev, 1979).

6. AQUATIC TOXICITY

6.1. ACUTE

Information concerning the acute toxicity of simazine to aquatic animals is available for at least 10 species of freshwater invertebrates, 13 species of freshwater fish and 3 species of saltwater invertebrates (Table 6-1).

There was a wide range in sensitivity among freshwater fish and invertebrates. The acute LC_{50} ranged between 1.0 and >100 mg/ℓ for invertebrates and between 0.25 and >180 mg/ℓ for fish. Although the available data indicate that there is a wide variation in species sensitivity, it is possible that some of the differences are due to the use of formulations of simazine that vary in toxicity. For instance, the lowest and highest LC_{50} values were both determined with striped bass fingerlings. Wellborn (1969) used a wettable powder formulation containing 80% simazine and reported a 96-hour LC_{50} of 0.25 mg/ℓ. McCann and Hitch (1980) attempted to replicate this test as closely as possible, but found no effects on striped bass at their highest test concentration of 180 mg/ℓ. Although both tests used 80% wettable powder formulations, there were clear differences in toxicity, perhaps due to differences in the additives used in the two formulations. Even though formulations may differ in toxicity, it is clear that there are real differences in species sensitivity. Sanders (1970) tested six invertebrate species with the same formulation and reported 48-hour LC_{50} values of 1.0 mg/ℓ for Daphnia magna and 3.2 mg/ℓ for Cypridopsis vidua. In contrast, four other species were not affected by 48 hours of exposure to 100 mg/ℓ.

The only available information concerning acute toxicity of simazine to marine organisms was provided by Portmann and Wilson (1971), who reported that no effects occurred in shrimp, crabs and snails exposed to 100 mg/ℓ (see Table 6-1).

TABLE 6-1

Acute Effects of Simazine on Aquatic Animals

Species	Duration (hours)	Concentration (mg/ℓ)	Effect	Reference
		FRESHWATER		
Waterflea				
Daphnia magna	48	1.0	LC_{50}	Sanders, 1970
Daphnia pulex	48	92.1	LC_{50}	Fitzmayer et al., 1982
Ostracod				
Cypridopsis vidua	48	3.2	LC_{50}	Sanders, 1970
Copepod				
Heliodiaptomas viduus	24	1.0	LC_{50}	George et al., 1982
Scuds				
Gammarus lacustris	96	13.0	LC_{50}	Sanders, 1969
Gammarus fasciatus	48	100.0	none	Sanders, 1970
Isopod				
Asellus brevicaudus	48	100.0	none	Sanders, 1970
Glass shrimp				
Palaemonetes kadiakensis	48	100.0	none	Sanders, 1970
Crayfish				
Orconectes nais	48	100.0	none	Sanders, 1970
Stonfly				
Pteronarcys californica	96	1.9	LC_{50}	Johnson and Finley, 1980
Rainbow Trout				
Salmo gairdneri	96	56	LC_{50}	Cope, 1965
	96	>100	LC_{50}	Johnson and Finley, 1980
Fathead minnow				
Pimephales promelas	96	>100	LC_{50}	Johnson and Finley, 1980
Bluegill				
Lepomis macrochirus	96	100	LC_{50}	Johnson and Finley, 1980
	96	118	LC_{50}	Cope, 1965

TABLE 6-1 (cont.)

Species	Duration (hours)	Concentration (mg/ℓ)	Effect	Reference
Striped bass *Morone saxatilis*	96 96	0.25 180.0	LC_{50} none	Wellborn, 1969 McCann and Hitch, 1980
Tilapia *Tilapia mossambica*	96	3.1	LC_{50}	Rao and Dad, 1979
Cyprinid *Puntius ticto*	96	24.5	LC_{50}	Rao and Dad, 1979
Zebrafish *Danio* sp.	96	12.6	LC_{50}	Upadhaya and Rao, 1980
Carp *Cyprinus carpio*	48	>40	LC_{50}	Hejduk and Svobodova, 1980
Goldfish *Carassius auratus*	48	>40	LC_{50}	Hejduk and Svobodova, 1980
Medaka *Oryzias latipes*	48	>40	LC_{50}	Hejduk and Svobodova, 1980
Pond loach	48	>40	LC_{50}	Hejduk and Svobodova, 1980
		SALTWATER		
Shrimp *Crangon crangon*	48	100	none	Portmann and Wilson, 1971
Crab *Carcinum maenas*	48	100	none	Portmann and Wilson, 1971
Snail *Cardium edule*	48	100	none	Portmann and Wilson, 1971

6.2. CHRONIC

The only available information concerning the chronic toxicity of simazine to aquatic animals was provided by Fitzmayer et al. (1982) who exposed waterfleas, Daphnia pulex, for 26 days to simazine concentrations of 0, 4 and 20 mg/ℓ. Survival, growth, maturation and reproduction were significantly inhibited at both simazine concentrations, relative to the controls. An MATC cannot be estimated because there was no test concentration that had no effect. For comparative purposes, the 48-hour LC_{50} for this species was 92 mg/ℓ (Fitzmayer et al., 1982).

Although no chronic studies with fish were available, Upadhaya and Rao (1980) exposed three species of fish to a simazine formulation for 15 days. The results from this subchronic study indicated that the lowest lethal levels were 1 mg/ℓ for Puntius ticto, 5 mg/ℓ for Tilapia mossambica and 10 mg/ℓ for Heteropneustes fossilis.

6.3. PLANT EFFECTS

Although simazine is used as an aquatic herbicide, the available information concerning the effects of simazine on aquatic plants is limited to a few laboratory studies and several field studies.

The EC_{50} of simazine has been determined for four species of algae (Walsh, 1972). The EC_{50}, based on oxygen evolution and growth, was 0.5-0.6 mg/ℓ for Isochrysis galbana and Phaeodactylum tricornutum, 2.0-2.5 mg/ℓ for Chlorococcum sp. and 4.0-5.0 mg/ℓ for Dunaliella tertiolecta. Mehta and Hawxly (1979) reported that the chlorophyll content of blue-green alga, Anacystis nidulans, was decreased by incubation with 10^{-5} M simazine. Simazine concentrations of $\geq$0.5 ppm inhibited growth of the green alga Chlamydomonas reinhardii (Carter, 1981). The only available laboratory data concerning the effects of simazine on aquatic macrophytes showed that

duckweed, Elodea canadensis, exposed for 72 hours were killed by 3 ppm simazine but not by 1 ppm (Dabydeen and Leavitt, 1981).

Field studies have shown that simazine is quite effective in controlling unicellular algae and macrophytic aquatic plants at concentrations between ~0.25 and 1.3 mg/ℓ. Patnaik and Ramachandron (1976) reported that 0.25 ppm controlled blooms of blue-green algae, Microcystis aeruginosa. Schreckenbach et al. (1981) found that a single treatment of 1 mg/ℓ controlled algae production. Tucker et al. (1983) reported that 1.3 mg/ℓ controlled the macrophytic alga Chara vulgaris. Similar results were reported by Crawford (1981) who found that simazine controlled Chara vulgaris as well as angiosperm macrophytes, Potamogeton sp. and Najas sp., in ponds.

The available laboratory and field data indicate that simazine is toxic to a wide variety of aquatic plants, and that all tested aquatic plant species were killed at concentrations of ≤5 ppm.

6.4. RESIDUES

Little information is available concerning the residues of simazine in aquatic animals after treatment with this chemical for aquatic plant control.

The bioaccumulation of ^{14}C-labeled simazine in mosquito fish, Gambusia affini, was studied in a freshwater micro-ecosystem (Isensee and Yockim, 1980). In a model static ecosystem, the BCF of simazine and its ^{14}C-labeled metabolites was found to vary between 19 and 50, whereas in a flowthrough system, the same parameter varied between 304 and 6765. The wide variation in the flowthrough system was due in part to a malfunction of the dosing apparatus. Thin-layer chromatography of fish homogenates showed that 30-74% and 100% of the radioactivity was in the form of metabolite in the static and flowthrough systems, respectively. Rogers (1970) reported

that green sunfish, Lepomis cyanellus, contained 0.95 and 2.29 ppm simazine after 3 weeks of exposure to 1 and 3 ppm, respectively. No simazine residues were detected in fish after 7 days in clean water. Mauck et al. (1976) investigated the residue dynamics of simazine in small ponds. They found that residue concentrations in bluegills generally did not exceed the concentrations of simazine in the water from which the fish were taken; however, low levels of simazine were detected in fish for ~1 year after the last pond treatment.

These results indicate that simazine probably has a low biocentration potential, but may persist in the aquatic environment for extended periods.

6.5. OTHER RELEVANT INFORMATION

Several investigators have studied the indirect effects of simazine as a result of its use as an aquatic herbicide. Treatment with simazine often results in periods of oxygen depletion as the killed algae and macrophytes decay. This oxygen depletion occurs with many other aquatic herbicides and may have adverse effects on the aquatic animals in a treated area if low oxygen conditions are severe enough. Patnaik and Ramachandran (1976) reported that ponds treated with 0.25 ppm simazine controlled algae and caused a marked drop in dissolved oxygen during the first few days after treatment; however, there were no observed effects on the animal populations. In contrast, Tucker et al. (1983) reported that three simazine treatments of channel catfish culture ponds totalling 1.3 mg/L caused an extended period of low oxygen concentrations and a 20% reduction in catfish production. A single treatment with 1.5 mg/L in ponds used for bluegill production caused oxygen depletion, but no change in fish yield. Similarly, Harmon (1978) reported that application of 0.5 ppm simazine to a lake killed the algae and resulted in a biomass reduction in two snail species even

though laboratory tests showed that these snails tolerated acute 96-hour exposure to as much as 5.0 ppm. Schreckenbach et al. (1981) used a single treatment of 1 mg/ℓ to control algae in carp production ponds and found that this treatment resulted in stabilization of pH at 6.5-7.5 and prevention of ammonia buildup, both of which led to a lower incidence of disease among the carp.

7. GUIDELINES AND STANDARDS

7.1. HUMANS

The U.S. EPA has established the following tolerances for simazine residues in raw agricultural commodities: 0.02 ppm in milk and meat; 0.20-0.25 ppm in some fruits, nuts and vegetables; 10 ppm in asparagus; 12 ppm in fish; and 15 ppm in alfalfa (Code of Federal Regulations, 1982).

7.2. AQUATIC

Existing guidelines or standards for protection of non-target aquatic organisms from simazine effects were not found in the literature searched.

8. RISK ASSESSMENT

Simazine was tested for carcinogenicity in conjunction with atrazine, as the herbicidal formulation Fogard S, which contains 37.5% simazine and 25% atrazine (active ingredients) (Donna et al., 1981). A total dose of 0.0065 mg of the active ingredients was administered to mice either subcutaneously or intraperitoneally as 13 injections at 3-day intervals. Malignant lymphomas were seen in both exposure groups, while a single incidence of peritoneal mesothelioma also was observed following subcutaneous administration. Due to the mixed exposures and small numbers of animals tested (25/treated group, 50/control group), no conclusion regarding the carcinogenicity of simazine can be drawn from this study.

Simazine has been tested for genotoxicity in many prokaryotic and eucaryotic systems, but positive results have been obtained only in gene mutation assays in eucaryotic systems (see Table 5-1).

Depressed fetal weight and a decreased degree of caudel ossification were observed in the fetuses of rats exposed to simazine aerosols of 17, 77 or 317 mg/m^3 for 2 hours/day on days 7-14 of gestation (Dilley et al., 1977; Newell and Dilley, 1978). Treatment at these levels did not result in evidence of either teratogenicity or maternal toxicity.

When administered per os as a single dose of 1000 mg/kg bw to mice, simazine did not inhibit testicular DNA synthesis (Seiler, 1977).

Dshurov (1979) examined the effects of subchronic oral administration of simazine under various dose regimes to sheep. Treatment-related effects were seen principally in the CNS, kidneys, liver, thyroid and reproductive organs. The lack of details regarding effects, dose-response relationship

and use of control animals in this Bulgarian study, and the fact that ruminants are not a good model for predicting toxicity to humans preclude the use of this study in quantitative risk assessment for humans.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment can, however, be presented in this chapter.

The CBI Appendix to this document reviews other animal studies, but these data are also inadequate for quantitative risk assessment.

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APPENDIX: LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE

These searches were conducted in July and August, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

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